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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/917,154	MONAHAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 November 2003 has been entered.

Claims 1-20 are pending. Claims 19 and 20 are withdrawn from consideration and claims 1-18 were previously considered. Claims 1-3, 5-10 and 13-18 were amended in the 17 November Paper. Claims 1-18 are presently under consideration.

Priority

In the Office Action mailed 11 March 2003 and again in the Office Action mailed 16 July 2003, the Examiner requested that the first line of the specification be amended to indicate that the instant application claims benefit of U.S. application 08/571,536, which is presently identified only by the serial number of the patent issued from the application (i.e., 6,265,387). Applicant is again urged to amend the specification to properly indicate that the present application claims benefit of a U.S. patent application, not a U.S. patent.

In the 17 November Paper, the specification was amended to claim benefit of U.S. Serial No. 09/707,000 and U.S. Serial No. 09/707,117. As stated in previous Office Actions, if the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior

application (see 37 CFR § 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 USC § 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 USC § 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 USC 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR § 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional.

As the instant application was filed after 29 November 2000 and the priority claim was not made within the acceptable time period, the instant application may not receive benefit of U.S. Serial No. 09/707,000 and U.S. Serial No. 09/707,117 unless the priority claim is accompanied by a grantable petition (*Id.*).

Specification

In the Office Action mailed 11 March 2003, the Examiner objected to the specification as containing sequence disclosures that are not accompanied by sequence identifier numbers (SEQ ID NO) that refer back to the sequence listing (e.g., page 45, line 12; page 49, line 9; page 54, line 16). In response, Applicant filed a proper sequence listing and CRF but failed to amend the specification as requested. Thus, the specification stands objected to and Applicant is required to

respond to this Office Action by amending the specification to properly identify all sequences disclosed therein by SEQ ID NO.

Response to Amendment

Double Patenting

Rejection of claims 8-15 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-14 of U.S. Patent No. 6,379,966 is withdrawn in view of the amendments to the claims such that they are now limited to inserting the complex into a blood vessel of a limb and applying pressure to the limb epidermis.

Provisional rejection of claims 1-7 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 9, 11 and 12 of copending Application No. 09/319,260 is rendered moot by abandonment of the '260 application.

Provisional rejection of claims 1-7, 17 and 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19, 20 and 22 of copending application 09/447,966 is withdrawn in view of the amendments to the claims such that they are now limited to inserting the polynucleotide into a blood vessel of a limb and applying pressure to the limb epidermis.

Claims 1-7 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 and 37-39 of

copending Application No. 09/707,000. Applicant has indicated that a terminal disclaimer will be filed upon allowance of the claims.

Claim Rejections - 35 USC § 102

Rejection of claims 1-5, 7-13, 15 and 17 under 35 U.S.C. §102 as anticipated by either one of US Patent No. 5,328,470 or US Patent No. 5,698,531 is withdrawn in view of the amendments to the claims such that they are now limited to inserting the polynucleotide into a blood vessel of a limb and applying pressure to the limb epidermis. The art of record does not teach or suggest these limitations.

Claim Rejections - 35 USC § 103

Rejection of claims 1-18 under 35 U.S.C. 103(a) as being unpatentable over each of US Patent No. 5,328,470 and US Patent No. 5,698,531 in view of US Patent No. 5,026,558 is withdrawn in view of the amendments to the claims such that they are now limited to inserting the polynucleotide or complex into a blood vessel of a limb and applying pressure to the limb epidermis (*Id.*).

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

In the instant case, the claims have been amended such that they are now limited to inserting a polynucleotide or complex into a blood vessel of a limb and applying pressure to the limb epidermis. In addition, claim 17 has been amended such that it is now limited to a process additionally comprising administering an immunosuppressive treatment. In the remarks that

accompany the amendment, Applicant indicates that support for the amendments can be found in copending applications 09/707,117 and 09/707,000, to which Applicant has sought benefit. However, even if the priority claim had been proper, a priority claim under 35 U.S.C. 120 does not amount to an incorporation by reference of the application(s) to which priority is claimed (M.P.E.P. 201.06(c)). Thus, the disclosure of 09/707,117 and 09/707,000 applications cannot be relied upon as support for limitations not present in the instant application as originally filed unless those applications were incorporated by reference at the time of filing.

As the claims are not fully supported by the disclosures of those applications to which priority is properly claimed, the effective filing date of the instant claims is 27 July 2001 (i.e., the actual filing date of the instant application).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite in the recitation of "the limb" in step (c). There is no antecedent basis for "the limb" in the claim.

Claims 9-18 are indefinite insofar as they depend from claim 8.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6, 7 and 18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 32-34 of copending Application No. 09/707,117.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '117 application are directed to species fully embraced by the instant claims. Claim 5 of the '117 application, which depends from claim 1, is directed to a method for delivering a polynucleotide into a limb skeletal muscle cell in a mammal comprising inserting the polynucleotide into a blood vessel, applying pressure to the limb epidermis to impede blood flow, applying immunosuppression and delivering the polynucleotide into the skeletal muscle cell. The instant claim 1 is more generally directed to a process for delivering a polynucleotide into a parenchymal cell in a mammalian limb comprising inserting a polynucleotide into a blood vessel of the limb, applying pressure to the limb epidermis to impede blood flow and delivering the polynucleotide into the parenchymal cell. Thus, the instant claims merely expand the scope of the '117 application claims in a nonspecific manner and the instant claims would be anticipated by the claims of the '117 application. Furthermore, the instant claim 7, which limits the limb to a leg, is anticipated by claim 6 of the '117 application, which limits

the limb muscle cell of claim 5 to a leg muscle cell; and the instant claims 6 and 18, which limit the applying pressure to applying an external cuff selected from a tourniquet and a sphygmomanometer, is anticipated by claims 32-34, which recite the same limitations.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-5 and 16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 5 of copending Application No. 09/707,117 (*supra*) in view of Budker *et al.* (1998) *Gene Ther.* 5:272-6.

As described above, the limitations of the instant claim 1 are anticipated by claims 1 and 5 of the '117 application. The process of the instant claims 2-5 is further limited to increasing the permeability of the blood vessels as a result of inserting the polynucleotide. Although this limitation is not recited in the claims of the '117 application, claims 2-5 as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the application was filed in view of the teachings of Budker *et al.*

Budker *et al.* teaches a process of delivering a nucleic acid into a limb of a mammal wherein permeability of blood vessels in the limb are increased as a consequence of the inserting the nucleic acid according to claim 2, wherein increasing permeability consists of increasing a volume of fluid within the limb according to claim 3 by inserting a solution containing the polynucleotide according to claim 4, wherein permeability is controlled by altering the rate of insertion of the volume into the vessel according to claim 5, and wherein the polynucleotide is inserted in at least 1 milliliter solution according to claim 16 (see especially Figures 1 and 2 and

the captions thereto; and the discussions in the paragraphs bridging columns 1 and 2 on page 272 and bridging 274-276).

Thus, the method steps set forth in the instant claims 2-5 were known to one of ordinary skill in the art at the time of filing. Furthermore, the skilled artisan would have been motivated to modify the claims of the '117 application to include the limitations taught by Budker *et al.* in view of the teachings of Budker *et al.* that intra-arterial delivery of plasmid DNA to muscle can be greatly enhanced by increasing intravascular hydrostatic pressure (see especially the paragraph bridging pages 274-276). Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings of Budker *et al.* with the claim limitations of the '117 application because the teachings of Budker *et al.* demonstrates the effectiveness of the method disclosed therein, which differs from the method disclosed in the '117 application only in the method of impeding fluid flow.

This is a provisional obviousness-type double patenting rejection.

Claims 8-16 and 18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 32-34 of copending Application No. 09/707,117 in view of Budker *et al.* (*supra*) and further in view of Thierry *et al.* (2000) US Patent No. 6,096,335.

The process of the instant claims 8-16 and 18 is the same as the instant claims 1-7 and 18 except that the process is further limited to making a polynucleotide-compound complex wherein the zeta potential of the complex is less negative than the polynucleotide alone and adding another compound to the complex to increase zeta potential negativity of the complex. Thus, the

limitations of the process of claims 8-16 and 18 are obvious over the teachings of the '117 application in view of Budker *et al.* except for the steps recited for making the complex.

Thierry *et al.* teaches a process for producing a stable complex for delivery of a nucleic acid into a mammal *in vivo*. In column 8, Thierry *et al.* teaches that a complex is formed by mixing a globally anionic biologically active substance, preferably DNA, with a complex formed from a cationic and anionic constituent. In column 6, lines 35-47, Thierry *et al.* teaches that the complexes formed may have positive charge ratios, and thus may have a less negative zeta potential than a nucleic acid. Further, in column 10, lines 1-15, Thierry *et al.* teaches that polyanions, which would increase the zeta potential negativity, can be added to the complexes to improve the transport potential of the lipoplexes.

In view of the teachings of Thierry *et al.*, it would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method set forth in the claims of copending application '717 as modified by the teachings of Budker *et al.* to incorporate the method of making complexes taught by Thierry *et al.* Motivation to combine these teachings comes from Thierry *et al.* who teaches that the complexes described therein are effective for delivering nucleic acids *in vivo*. In particular, Thierry *et al.* teaches in column 3:

> "The invention concerned here is designed to provide a transport system for active agents, and nucleic acids in particular, free of the disadvantages of earlier systems. The formulation of the invention notably enables optimal gene transfer, since it offers the advantages listed below which form the basis of effective transfection:
>
> Condensation of DNA.
>
> Protection of DNA against nucleases.
>
> Improved plasma half-life, via decreased interaction with blood cells or plasma proteins.

Transport in DNA target.

Release of DNA in cytoplasm and nucleoplasm.

Cell targeting ability"

Thus, the skilled artisan would be motivated to include the complexes taught by Thierry *et al.* in the method claimed in the '717 application to obtain the many benefits described by Thierry *et al.* Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Thierry *et al.* demonstrates the effectiveness of the complexes disclosed therein in delivering a nucleic acid to cells *in vivo* (see especially Example 9).

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Milas *et al.* (1997) *Clin. Cancer Res.* 3:2197-2203.

Milas teaches a process of delivering a polynucleotide into a parenchymal cell in a mammalian limb *in vivo* comprising inserting the polynucleotide into a blood vessel of the limb, applying pressure to the limb epidermis to impede fluid flow in the vessel and delivering the poly nucleotide into the parenchymal cell (see especially Figure 1 and Figure 4 and the captions

thereto). Thus, Milas teaches a process comprising all of the steps of the instant claim 1. Milas further teaches the process wherein applying pressure consists of applying an external cuff according to claim 6, which is a tourniquet according to claim 18 (see especially Figure 1 and the section entitled "Operative Technique: Isolated Limb Perfusion" beginning in the right column on page 2198). As Milas *et al.* teaches a process comprising all of the limitations of the instant claims, the claims are anticipated by Milas *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Budker *et al.* (*supra*) in view of Milas *et al.* (*supra*).

Budker *et al.* teach a process for delivering a polynucleotide into a parenchymal cell in a mammalian limb comprising inserting a polynucleotide into a blood vessel of the limb, applying pressure to blood vessels in the limb to impede blood flow and delivering the polynucleotide into the parenchymal cell (see especially Figures 1 and 2 and the captions thereto). Thus, Budker teaches all of the limitations of the process set forth in the instant claim 1 except for applying pressure to the epidermis of the mammal.

As described above, Milas teaches the method of the instant claim wherein blood flow is impeded by application of a tourniquet to the limb epidermis of the mammal.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the teachings of Budker *et al.* to include the step of applying pressure to the limb epidermis according to the method of Milas *et al.* according to the limitations of the instant claim 1. The skilled artisan would have been motivated to combine these teachings in view of the relative simplicity of isolating a limb from the systemic circulation by an external tourniquet, and in view of teachings from Milas *et al.* indicating that the limb was effectively isolated by the tourniquet. For example Milas *et al.* teaches that, "[t]he perfusate remained highly concentrated in the isolated limb with minimal systemic leakage rate" (second full paragraph in the left column on page 2201; see also the first full paragraph in the right

column on page 2201). Absent evidence to the contrary, one would also have a reasonable expectation of success in combining these teachings in view of the demonstrated effectiveness of the external tourniquet. Thus, the process of independent claim 1, as a whole, would have been obvious to one of ordinary skill at the time of filing.

As described above, Budker *et al.* further teaches the method comprising each of the limitations of claims 2-5, 7 and 16. To summarize, Budker teaches a process of delivering a nucleic acid into a limb of a mammal wherein permeability of blood vessels in the limb are increased as a consequence of the inserting the nucleic acid according to claim 2, wherein increasing permeability consists of increasing a volume of fluid within the limb according to claim 3 by inserting a solution containing the polynucleotide according to claim 4, wherein permeability is controlled by altering the rate of insertion of the volume into the vessel according to claim 5, and wherein the polynucleotide is inserted in at least 1 milliliter solution according to claim 16 (see especially Figures 1 and 2 and the captions thereto; and the discussions in the paragraphs bridging columns 1 and 2 on page 272 and bridging pages 274-276).

Also as described above, Milas *et al.* further teaches the process wherein applying pressure consists of applying an external cuff according to claim 6, which is a tourniquet according to claim 18 (see especially Figure 1 and the section entitled "Operative Technique: Isolated Limb Perfusion" beginning in the right column on page 2198).

Thus, a method comprising each of the limitations of dependent claims 2-7, 16 and 18 would also have been obvious to one of ordinary skill in the art at the time the application was filed. Therefore, the invention of claims 1-7, 16 and 18, as a whole would have been *prima facie* obvious to one of ordinary skill at the time of filing.

Claims 1-7, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stedman *et al.* (filed 21 October 1997) US Patent No. 6,177,407 in view of Milas *et al.* (*supra*).

Stedman *et al.* teaches a process for delivering a polynucleotide into a parenchymal cell in a mammalian limb comprising inserting a polynucleotide into a blood vessel of the limb, applying pressure to blood vessels in the limb to impede blood flow and delivering the polynucleotide into the parenchymal cell (see especially column 3, lines 25-29 and 44-64; Figure 7 and the caption thereto; and column 12, third full paragraph). Stedman *et al.* further teaches that any method of occluding flow through a blood vessel may be used, and explicitly contemplates various methods (see especially the second full paragraph in column 13). Stedman *et al.* thus contemplates all of the limitations of the instant independent claim 1 but does not explicitly teach applying pressure to the limb epidermis to impede flow.

As described above, Milas teaches the method of the instant claim wherein blood flow is impeded by application of a tourniquet to the limb epidermis of the mammal.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to modify the teachings of Stedman *et al.* to include the step of applying pressure to the limb epidermis according to the method of Milas *et al.* according to the limitations of the instant claim 1. The skilled artisan would have been motivated to combine these teachings in view of the teachings of Stedman *et al.* indicating that any method of occluding flow may be used (*Id.*), the relative simplicity of isolating a limb from the systemic circulation by an external tourniquet, and in view of teachings from Milas *et al.* indicating that the limb was effectively isolated by the tourniquet. For example Milas *et al.* teaches that, "[t]he

perfusate remained highly concentrated in the isolated limb with minimal systemic leakage rate" (*supra*). Absent evidence to the contrary, one would also have a reasonable expectation of success in combining these teachings in view of the demonstrated effectiveness of the external tourniquet. Thus, the process of independent claim 1, as a whole, would have been obvious to one of ordinary skill at the time of filing.

Stedman *et al.* further teaches the method comprising each of the limitations of claims 2-5, 7 and 16. Stedman *et al.* teaches a process of delivering a nucleic acid into a limb of a mammal wherein permeability of blood vessels in the limb is increased as a consequence of inserting the nucleic acid according to claim 2, wherein increasing permeability consists of increasing a volume of fluid within the limb according to claim 3 by inserting a solution containing the polynucleotide according to claim 4, wherein permeability is controlled by altering the rate of insertion of the volume into the vessel according to claim 5, and wherein the polynucleotide is inserted in at least 1 milliliter solution according to claim 16 (see especially column 3, lines 25-29 and 44-64; Figure 7 and the caption thereto; and column 12, third full paragraph).

Also as described above, Milas *et al.* further teaches the process wherein applying pressure consists of applying an external cuff according to claim 6, which is a tourniquet according to claim 18 (see especially Figure 1 and the section entitled "Operative Technique: Isolated Limb Perfusion" beginning in the right column on page 2198).

Thus, a method comprising each of the limitations of dependent claims 2-7, 16 and 18 would also have been obvious to one of ordinary skill in the art at the time of filing. Therefore,

the invention of claims 1-7, 16 and 18, as a whole would have been *prima facie* obvious to one of ordinary skill at the time the application was filed.

Claims 8-16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stedman *et al.* (*supra*) in view of Milas *et al.* (*supra*) and further in view of Thierry *et al.* (*supra*).

As described previously, the process of the instant claims 8-16 and 18 is the same as the instant claims 1-7 and 18 except that the process is further limited to making a polynucleotide-compound complex wherein the zeta potential of the complex is less negative than the polynucleotide alone and adding another compound to the complex to increase zeta potential negativity of the complex. Thus, the limitations of the process of claims 8-16 and 18 are obvious over the teachings of the Stedman *et al.* in view of Milas *et al.*, except for the steps recited for making the complex, for the reasons set forth herein above.

Thierry *et al.* teaches a process for producing a stable complex for delivery of a nucleic acid into a mammal *in vivo*. In column 8, Thierry *et al.* teaches that a complex is formed by mixing a globally anionic biologically active substance, preferably DNA, with a complex formed from a cationic and anionic constituent. In column 6, lines 35-47, Thierry *et al.* teaches that the complexes formed may have positive charge ratios, and thus may have a less negative zeta potential than a nucleic acid. Further, in column 10, lines 1-15, Thierry *et al.* teaches that polyanions, which would increase the zeta potential negativity, can be added to the complexes to improve the transport potential of the lipoplexes.

In view of the teachings of Thierry *et al.*, it would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the method set forth in Stedman *et al.* and Milas *et al.* to incorporate the method of making complexes taught by Thierry *et al.* Motivation to combine these teachings comes from Thierry *et al.* who teaches that the complexes described therein are effective for delivering nucleic acids *in vivo*. In particular, Thierry *et al.* teaches in column 3:

> "The invention concerned here is designed to provide a transport system for active agents, and nucleic acids in particular, free of the disadvantages of earlier systems. The formulation of the invention notably enables optimal gene transfer, since it offers the advantages listed below which form the basis of effective transfection:
>
> Condensation of DNA.
>
> Protection of DNA against nucleases.
>
> Improved plasma half-life, via decreased interaction with blood cells or plasma proteins.
>
> Transport in DNA target.
>
> Release of DNA in cytoplasm and nucleoplasm.
>
> Cell targeting ability"

Thierry *et al.* teaches that the complexes described therein are particularly advantageous as compared to the adenovirus vectors used by Stedman *et al.* because of the toxicity associated with viral vectors (see especially column 1, lines 34-41).

Thus, the skilled artisan would be motivated to include the complexes taught by Thierry *et al.* in the method of Stedman *et al.* in view of Milas *et al.* to obtain the many benefits described by Thierry *et al.* Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because Thierry *et al.* demonstrates the

effectiveness of the complexes disclosed therein in delivering a nucleic acid to cells *in vivo* (see especially Example 9).

Thus, the invention of claims 8-16 and 18 as a whole would have been *prima facie* obvious to on of ordinary skill in the art at the time of filing.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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DMS

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